TAXOL®
(paclitaxel) Injection

Brief Summary of Prescribing Information, 12/97. For complete prescribing information, please consult official package circular.

INDICATIONS
TAXOL is indicated, after failure of first-line or subsequent chemotherapy for the treatment of metastatic carcinoma of the ovary.

TAXOL is indicated for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated.

TAXOL is indicated for the second-line treatment of AIDS-related Kaposi's sarcoma.

CONTRAINDICATIONS
TAXOL is contraindicated in patients who have a history of hypersensitivity reactions to TAXOL or other drugs formulated in Cremophor® EL (polyoxyethylated castor oil).

TAXOL should not be used in patients with solid tumors who have baseline neutrophil counts of < 1500 cells/mm³ or in patients with AIDS-related Kaposi's sarcoma with baseline neutrophil counts of < 1000 cells/mm³.

WARNINGS
Anaphylaxis and severe hypersensitivity reactions characterized by dyspnea and hypotension requiring treatment, angioedema, and generalized urticaria have occurred in 2% of patients receiving TAXOL in clinical trials. Fatal reactions have occurred in patients despite premedication. All patients should be pretreated with corticosteroids, diphenhydramine, and H_2 antagonists. (See "DOSAGE AND ADMINISTRATION" section.) Patients who experience severe hypersensitivity reactions to TAXOL should not be rechallenged with the drug.

Bone marrow suppression (primarily neutropenia) is dose-dependent and is the dose-limiting toxicity. Neutrophil nadirs occurred at a median of 11 days. TAXOL should not be administered to patients with baseline neutrophil counts of less than 1500 cells/mm³ (<1000 cells/mm³ for patients with KS). Frequent monitoring of blood counts should be instituted during TAXOL treatment. Patients should not be re-treated with subsequent cycles of TAXOL until neutrophils recover to a level >1500 cells/mm³ (>1000 cells/mm³ for patients with KS) and platelets recover to a level >100,000 cells/mm³.

Severe conduction abnormalities have been documented in <1% of patients during TAXOL therapy and in some cases requiring pacemaker placement. If patients develop significant conduction abnormalities during TAXOL infusion, appropriate therapy should be administered and continuous cardiac monitoring should be performed during subsequent therapy with TAXOL.

Pregnancy: TAXOL can cause fetal harm when administered to a pregnant woman. Administration of paclitaxel during the period of organogenesis to rabbits at doses of 3.0 mg/kg/day (about 0.2 the daily maximum recommended human dose on a mg/m² basis) caused embryo-and fetotoxicity, as indicated by intrauterine mortality, increased resorptions and increased fetal deaths. Maternal toxicity was also observed at this dose. No teratogenic effects were observed at 1.0 mg/kg/day (about 1/15 the daily maximum recommended human dose on a mg/m² basis); teratogenic potential could not be assessed at higher doses due to extensive fetal mortality.

There are no adequate and well-controlled studies in pregnant women. If TAXOL is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

PRECAUTIONS
Contact of the undiluted concentrate with plasticized polyvinyl chloride (PVC) equipment or devices used to prepare solutions for infusion is not recommended. In order to minimize patient exposure to the plasticizer DEHP [di-(2-ethylhexyl)phthalate], which may be leached from PVC infusion bags or sets, diluted TAXOL solutions should preferably be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets.

TAXOL should be administered through an in-line filter with a microporous membrane not greater than 0.22 microns. Use of filter devices such as IVEX-2® filters which incorporate short inlet and outlet PVC-coated tubing has not resulted in significant leaching of DEHP.

Drug Interactions: In a Phase 1 trial using escalating doses of TAXOL (110-200 mg/m²) and cisplatin (50 or 75 mg/m²) given as sequential infusions, myelosuppression was more profound when TAXOL was given after cisplatin than with the alternate sequence (i.e., TAXOL before cisplatin). Pharmacokinetic data from these patients demonstrated a decrease in paclitaxel clearance of approximately 33% when TAXOL was administered following cisplatin.

The metabolism of TAXOL is catalyzed by cytochrome P450 isoenzymes CYP2C8 and CYP3A4. In the absence of formal clinical drug interaction studies, caution should be exercised when administering TAXOL concomitantly with known substrates or inhibitors of the cytochrome P450 isoenzymes CYP2C8 and CYP3A4. (See "CLINICAL PHARMACOLOGY" section.)

Potential interactions between paclitaxel, a substrate of CYP3A4 and protease inhibitors (ritonavir, saquinavir, indinavir, and nelfinavir), which are substrates and/or inhibitors of CYP3A4 have not been evaluated in clinical trials.

Reports in the literature suggest that plasma levels of doxorubicin (and its active metabolite doxorubicinol) may be increased when paclitaxel and doxorubicin are used in combination.

Hematology: TAXOL therapy should not be administered to patients with baseline neutrophil counts of less than 1,500 cells/mm³. In order to monitor the occurrence of myelotoxicity, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving TAXOL. Patients should not be re-treated with subsequent cycles of TAXOL until neutrophils recover to a level >1500 cells/mm³ and platelets recover to a level >100,000 cells/mm³. In the case of severe neutropenia (<500 cells/mm³ for seven days or more) during a course of TAXOL therapy, a 20% reduction in dose for subsequent courses of therapy is recommended.

For patients with advanced HIV disease and poor-risk AIDS-related Kaposi's sarcoma, TAXOL, at the recommended dose for this disease, can be initiated and repeated if the neutrophil count is at least 1000 cells/mm³.

Hypersensitivity Reactions: Patients with a history of severe hypersensitivity reactions to products containing Cremophor® EL (e.g., cyclosporin for injection concentrate and teniposide for injection concentrate) should not be treated with TAXOL. In order to avoid the occurrence of severe hypersensitivity reactions, all patients treated with TAXOL should be premedicated with corticosteroids (such as dexamethasone), diphenhydramine and H_2 antagonists (such as cimetidine or ranitidine). Minor symptoms such as flushing, skin reactions, dyspnea, hypotension or tachycardia do not require interruption of therapy. However, severe reactions, such as hypotension requiring treatment, dyspnea requiring bronchodilators, angioedema or generalized urticaria require immediate discontinuation of TAXOL and aggressive symptomatic therapy. Patients who have developed severe hypersensitivity reactions should not be rechallenged with TAXOL.

Cardiovascular: Hypotension, bradycardia, and hypertension have been observed during administration of TAXOL, but generally do not require treatment. Occasionally TAXOL infusions must be interrupted or discontinued because of initial or recurrent hypertension. Frequent vital sign monitoring, particularly during the first hour of TAXOL infusion, is recommended. Continuous cardiac monitoring is not required except for patients with serious conduction abnormalities. (See "WARNINGS" section.)

Nervous System: Although, the occurrence of peripheral neuropathy is frequent, the development of severe symptomatology is unusual and requires a dose reduction of 20% for all subsequent courses of TAXOL.

TAXOL contains dehydrated alcohol USP, 396 mg/mL; consideration should be given to possible CNS and other effects of alcohol. (See "PRECAUTIONS: Pediatric Use" section.)

Hepatic: There is evidence that the toxicity of TAXOL is enhanced in patients with elevated liver enzymes. Caution should be exercised when administering TAXOL (paclitaxel) Injection to patients with moderate to severe hepatic impairment and dose adjustments should be considered.

Injection Site Reaction: Injection site reactions, including reactions secondary to extravasation, were usually mild and consisted of erythema, tenderness, skin discoloration, or swelling at the injection site. These reactions have been observed more frequently with the 24-hour infusion than with the 3-hour infusion. Recurrence of skin reactions at a site of previous extravasation following administration of TAXOL at a different site, i.e., "recall", has been reported rarely.

Rare reports of more severe events such as phlebitis, cellulitis, induration, skin exfoliation, necrosis and fibrosis have been received as part of the continuing surveillance of TAXOL safety. In some cases the onset of the injection site reaction either occurred during a prolonged infusion or was delayed by a week to ten days.

A specific treatment for extravasation reactions is unknown at this time. Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration.

Carcinogenesis, Mutagenesis, Impairment of Fertility: The carcinogenic potential of TAXOL has not been studied.

Paclitaxel has been shown to be clastogenic *in vitro* (chromosome aberrations in human lymphocytes) and *in vivo* (micronucleus test in mice). Paclitaxel was not mutagenic in the Ames test or the CHO/HGPRT gene mutation assay.

Administration of paclitaxel prior to and during mating produced impairment of fertility in male and female rats at doses equal to or greater than 1 mg/kg/day (about 0.04 the daily maximum recommended human dose on a mg/m² basis). At this dose, paclitaxel caused reduced fertility and reproductive indices, and increased embryo- and fetotoxicity. (See "WARNINGS" section.)

Pregnancy: Pregnancy "Category D". (See "WARNINGS" section.)

Nursing Mothers: It is not known whether the drug is excreted in human milk. Following intravenous administration of carbon-14 labeled TAXOL to rats on days 9 to 10 postpartum, milk concentrations of radioactivity exceeded and declined in parallel with the plasma concentrations. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, it is recommended that nursing be discontinued when receiving TAXOL therapy.

Pediatric Use: The safety and effectiveness of TAXOL in pediatric patients have not been established.

There have been reports of central nervous system (CNS) toxicity in an ongoing investigational clinical trial in pediatric patients in which TAXOL was infused intravenously over 3 hours at doses ranging from 350 mg/m² to 420 mg/m². The toxicity is most likely attributable to the high dose of the ethanol component of the TAXOL vehicle given over a short infusion time. The use of concomitant antihistamines may intensify this effect. Although a direct effect of the paclitaxel itself cannot be discounted, the high doses used in this study (over twice the recommended adult dosage) must be considered in assessing the safety of TAXOL for use in this population.

ADVERSE REACTIONS
The following is based on the experience of 812 patients (493 with ovarian carcinoma and 319 with breast carcinoma) enrolled in 10 studies. Two hundred and seventy-five patients were treated in 8 Phase 2 studies with TAXOL doses ranging from 135 to 300 mg/m² administered over 24 hours (in 4 of these studies, G-CSF was administered as hematopoietic support). Three hundred and one patients were treated in the randomized Phase 3 ovarian carcinoma study which compared two doses (135 or 175 mg/m²) and two schedules (3 or 24 hours) of TAXOL. Two hundred and thirty-six patients with breast carcinoma received TAXOL (135 or 175 mg/m²) administered over 3 hours in a controlled study.

The following is an adverse event summary of percent incidence in 812 patients receiving TAXOL: **1.) Bone Marrow** - Neutropenia (<2,000/mm³) 90 and (<500/mm³) 52; Leukopenia (<4,000/mm³) 90 and (<1,000/mm³) 17; Thrombocytopenia (<100,000/mm³) 20 and (<50,000/mm³) 7; Anemia (<11 g/dL) 78 and (<8 g/dL) 16; Infections 30; Bleeding 14; Red Cell Transfusions 25; Platelet Transfusions 2; **2.) Hypersensitivity Reaction** (with premedication) - All 41; Severe 2; **3.) Cardiovascular** - Vital Sign Changes (during first 3 hours of infusion) Bradycardia (N=537) 3 and Hypotension (N=532) 12; Significant Cardiovascular Events 1; **4.) Abnormal ECG** - All Pts. 23; Pts. with normal baseline (N=559) 14; **5.) Peripheral Neuropathy** - Any symptoms 60; Severe symptoms 3; **6.) Myalgia/Arthralgia** - Any symptoms 60; Severe Symptoms 8; **7.) Gastrointestinal** - Nausea and vomiting 52; Diarrhea 38; Mucositis 31; **8.) Alopecia** - 87; **9.) Hepatic** (Pts. with normal baseline) - Bilirubin elevations (N=765) 7; Alkaline phosphatase elevations (N=575) 22; AST (SGOT) elevations (N=591) 19; **10.) Injection Site Reaction** - 13.

None of the observed toxicities were clearly influenced by age.

The following shows the frequency (based on worst course analysis) of important adverse events (as percent of patients) in the 85 patients with KS treated with two different TAXOL regimens (i.e., 135 mg/m² q3wk vs 100 mg/m² q2wk): **1.) Bone Marrow** - Neutropenia (<2,000/mm³) 100 vs 95 and (<500/mm³) 75 vs 35; Thrombocytopenia (<100,000/mm³) 52 vs 27 and (<50,000/mm³) 17 vs 5; Anemia (<11 g/dL) 86 vs 73 and (<8 g/dL) 34 vs 25; Febrile Neutropenia 55 vs 9; **2.) Opportunistic Infection** - Any 76 vs 54; Cytomegalovirus 45 vs 27; Herpes Simplex 38 vs 11; *Pneumocystis carinii* 14 vs 21; M. avium intracellulare 24 vs 4; Candidiasis, esophageal 7 vs 9; Cryptosporidiosis 7 vs 7; Cryptococcal meningitis 3 vs 2; Leukoencephalopathy — vs 2; **3.) Hypersensitivity Reaction** (with premedication) - All 14 vs 9; **4.) Cardiovascular** - Hypotension 17 vs 9; Bradycardia 3 vs —; **5.) Peripheral Neuropathy** - Any 79 vs 46; Severe 10 vs 2; **6.) Myalgia/Arthralgia** - Any 93 vs 48; Severe 14 vs 16; **7.) Gastrointestinal** - Nausea and Vomiting 69 vs 70; Diarrhea 90 vs 73; Mucositis 45 vs 20; **8.) Renal** (creatinine elevation) - Any 34 vs 18; Severe (grade III/IV) 7 vs 5; **9.) Discontinuation for drug toxicity** - 7 vs 16.

As demonstrated in this table, toxicity was more pronounced in the study utilizing TAXOL at a dose of 135 mg/m² every 3 weeks than in the study utilizing TAXOL at a dose of 100 mg/m² every 2 weeks. Notably, severe neutropenia (76% versus 35%), febrile neutropenia (55% versus 9%), and opportunistic infections (76% versus 54%) were more common with the former dose and schedule. The differences between the two studies with respect to dose escalation and use of hematopoietic growth factors, as described above, should be taken into account. (See "CLINICAL STUDIES: AIDS-Related Kaposi's Sarcoma" section.) Note also that only 20% of the 85 patients in these studies received concomitant treatment with protease inhibitors, whose effect on paclitaxel metabolism has not yet been studied.

The following discussion refers to the overall safety database of 812 patients with solid tumors treated in clinical studies. The frequency and severity of adverse events have been generally similar for patients receiving TAXOL for the treatment of ovarian or breast carcinoma or for Kaposi's sarcoma, but patients with AIDS-related Kaposi's sarcoma may have more frequent and severe hematologic toxicity, infections, and febrile neutropenia. These patients require a lower dose intensity and supportive care. (See "CLINICAL STUDIES: AIDS-Related Kaposi's Sarcoma" section.) In addition, rare events have been reported from the postmarketing experience or from other clinical studies; toxicities that were observed only in the population with Kaposi's sarcoma or that occurred with greater severity in this population are also described. The frequency and severity of important adverse events for the Phase 3 ovarian and breast carcinoma studies are presented in tabular form by treatment arm in the CLINICAL STUDIES section.

Hematologic: Bone marrow suppression was the major dose-limiting toxicity of TAXOL. Neutropenia, the most important hematologic toxicity, was dose and schedule dependent and was generally rapidly reversible. Among patients treated in Phase 3 ovarian study with a 3-hour infusion, neutrophil counts decline below 500 cells/mm³ in 13% of the patients treated with a dose of 135 mg/m² compared to 27% at a dose of 175 mg/m² (p=0.05). In the same study, severe neutropenia (<500 cells/mm³) was more frequent with the 24-hour than with the 3-hour infusion; infusion duration had a greater impact on myelosuppression than dose. Neutropenia did not appear to increase with cumulative exposure and did not appear to be more frequent nor more severe for patients previously treated with radiation therapy.

Fever was frequent (12% of all treatment courses). Infectious episodes occurred in 30% of all patients and 9% of all courses; these episodes were fatal in 1% of all patients, and included sepsis, pneumonia and peritonitis. In the Phase 3 ovarian study, infectious episodes were reported in 19% of the patients given either 135 or 175 mg/m² dose by a 3-hour infusion. Urinary tract infections and upper respiratory tract infections were the most frequently reported infectious complications. In the immunosuppressed patient population with advanced HIV disease and poor-risk AIDS-related Kaposi's sarcoma, 61% of the patients reported at least one opportunistic infection. (See "CLINICAL STUDIES: AIDS-Related Kaposi's Sarcoma" section.) The use of supportive therapy, including G-CSF, is recommended for patients who have experienced severe neutropenia. (See "DOSAGE AND ADMINISTRATION" section.)

Thrombocytopenia was uncommon, and almost never severe (<50,000 cells/mm³). Twenty percent of the patients experienced a drop in their platelet count below 100,000 cells/mm³ at least once while on treatment; 7% had a platelet count <50,000 cells/mm³ at the time of their worst nadir. Among the 812 patients, bleeding episodes were reported in 4% of all courses and by 14% of all patients but most of the hemorrhagic episodes were localized and the frequency of these events was unrelated to the TAXOL dose and schedule. In the Phase 3 ovarian study, bleeding episodes were reported in 10% of the patients receiving either the 135 or 175 mg/m² dose given by a 3-hour infusion; no patients treated with the 3-hour infusion received platelet transfusions.

Anemia (Hb <11 g/dL) was observed in 78% of all patients and was severe (Hb <8 g/dL) in 16% of the cases. No consistent relationship between dose or schedule and the frequency of anemia was observed. Among all patients with normal baseline hemoglobin, 69% became anemic on study but only 7% had severe anemia. Red cell transfusions were required in 25% of all patients and in 12% of those with normal baseline hemoglobin levels.

Hypersensitivity Reactions (HSRs): All patients received premedication prior to TAXOL (see "WARNINGS" and "PRECAUTIONS: Hypersensitivity Reactions" sections). The frequency and severity of HSRs were not affected by the dose or schedule of TAXOL administration. In the Phase 3 ovarian study the 3-hour infusion was not associated with a greater increase in HSRs when compared to the 24-hour infusion. Hypersensitivity reactions were observed in 20% of all courses and in 41% of all patients. These reactions were severe in less than 2% of the patients and 1% of the courses. No severe reactions were observed after course 3 and severe symptoms occurred generally within the first hour of TAXOL (paclitaxel) Injection infusion. The most frequent symptoms observed during these severe reactions were dyspnea, flushing, chest pain and tachycardia.

The minor hypersensitivity reactions consisted mostly of flushing (28%), rash (12%), hypotension (4%), dyspnea (2%), tachycardia (2%) and hypertension (1%). The frequency of hypersensitivity reactions remained relatively stable during the entire treatment period.

Rare reports of chills and reports of back pain in association with hypersensitivity reactions have been received as part of the continuing surveillance of TAXOL safety.

Cardiovascular: Hypotension, during the first 3 hours of infusion, occurred in 12% of all patients and 3% of all courses administered. Bradycardia, during the first 3 hours of infusion, occurred in 3% of all patients and 1% of all courses. In Phase 3 ovarian study, neither dose nor schedule had an effect on the frequency of hypotension and bradycardia. These vital sign changes most often [illegible] therapy nor treatment discontinuation. [illegible] not influenced by prior anthracycline therapy.

Significant cardiovascular events [illegible] 1% of all patients. These events included [illegible] venous thrombosis. One of the patients [illegible] over 24 hours had progressive hypotension [illegible] asymptomatic ventricular tachycardia, [illegible] pacemaker placement.

Electrocardiogram (ECG) abnormalities [illegible] abnormalities on study did not usually [illegible] required no intervention. ECG abnormalities [illegible] patients with a normal ECG prior to study [illegible] tracing while on study. The most frequently [illegible] repolarization abnormalities, sinus bradycardia [illegible] Among patients with normal ECGs at baseline [illegible] influence the frequency of ECG abnormalities.

Cases of myocardial infarction have been reported [illegible] been reported typically in patients who [illegible] anthracyclines. (See "PRECAUTIONS: Drug Interactions" [illegible]

Rare reports of atrial fibrillation and supraventricular [illegible] part of the continuing surveillance of TAXOL safety.

Respiratory: Rare reports of interstitial [illegible] embolism have been received as part of the [illegible] reports of radiation pneumonitis have been [illegible] radiotherapy.

Neurologic: The frequency and severity of [illegible] dependent, but were not influenced by [illegible] observed in 60% of all patients (3% severe) and [illegible] pre-existing neuropathy.

The frequency of peripheral neuropathy [illegible] symptoms were observed in 27% of the patients [illegible] 34-51% from course 2 to 10.

Peripheral neuropathy was the cause of TAXOL [illegible] Sensory symptoms have usually improved [illegible] discontinuation. The incidence of neurologic [illegible] patients previously treated with cisplatin [illegible] therapies are not a contraindication for TAXOL therapy.

Other than peripheral neuropathy, [illegible] administration have been rare (<1%) and [illegible] ataxia and neuroencephalopathy.

Rare reports of autonomic neuropathy [illegible] part of the continuing surveillance of TAXOL [illegible] (scintillating scotomata) have also been reported [illegible] higher doses than those recommended. [illegible] However, rare reports in the literature of [illegible] suggested persistent optic nerve damage.

Arthralgia/Myalgia: There was no consistent [illegible] TAXOL and the frequency or severity of arthralgia/myalgia [illegible] treated experienced arthralgia/myalgia, 8% experienced [illegible] were usually transient, occurred two or three days [illegible] resolved within a few days. The frequency and severity of [illegible] remained unchanged throughout the treatment period.

Hepatic: No relationship was observed between [illegible] dose or schedule of TAXOL administration. Among patients [illegible] function 7%, 22% and 19% had elevations in bilirubin, [illegible] (SGOT), respectively. Prolonged exposure to TAXOL [illegible] hepatic toxicity.

Rare reports of hepatic necrosis and hepatic encephalopathy [illegible] received as part of the continuing surveillance of TAXOL safety.

Renal: Among the patients treated for Kaposi's sarcoma [illegible] toxicity of grade III or IV severity. One patient with [illegible] severity had to discontinue therapy. The other four [illegible] reversible elevations of serum creatinine.

Gastrointestinal (GI): Nausea/vomiting, diarrhea and [illegible] 38% and 31% of all patients, respectively. These [illegible] moderate. Mucositis was schedule dependent and [illegible] hour than with the 3-hour infusion.

In patients with poor-risk AIDS-related Kaposi's sarcoma [illegible] mucositis were reported by 69%, 79%, and 28% of patients [illegible] patients with Kaposi's sarcoma complained of diarrhea [illegible] STUDIES: AIDS-Related Kaposi's Sarcoma" section.)

Rare reports of intestinal obstruction, intestinal perforation, [illegible] and dehydration have been received as part of the continuing [illegible] Rare reports of neutropenic enterocolitis (typhlitis) [illegible] were observed in patients treated with TAXOL [illegible] chemotherapeutic agents.

Injection Site Reaction: Injection site reactions, [illegible] extravasation, were usually mild and consisted of erythema, [illegible] or swelling at the injection site. These reactions have [illegible] the 24-hour infusion than with the 3-hour infusion. [illegible] of previous extravasation following administration of [illegible] has been reported rarely.

Rare reports of more severe events such as phlebitis, [illegible] exfoliation, necrosis and fibrosis have been received as part [illegible] of TAXOL safety. In some cases the onset of the injection [illegible] during a prolonged infusion or was delayed by a week to ten days.

A specific treatment for extravasation reactions [illegible] possibility of extravasation, it is advisable to closely [illegible] infiltration during drug administration.

Other Clinical Events: Alopecia was observed in almost [illegible] skin changes due to TAXOL-related hypersensitivity reactions, [illegible] other skin toxicities were significantly associated with [illegible] (changes in pigmentation or discoloration of nail bed) [illegible] reported in 21% of all patients (17% of those without [illegible] edema and none of these patients required treatment [illegible] commonly local and disease-related. Edema was observed [illegible] with normal baseline and did not increase with time on [illegible]

Rare reports of skin abnormalities related to [illegible] maculopapular rash and pruritus have been received as [illegible] of TAXOL safety.

Reports of asthenia and malaise have been received [illegible] of TAXOL safety.

Accidental Exposure: Upon inhalation, dyspnea, chest [illegible] nausea have been reported. Following topical exposure [illegible] burning and redness.

OVERDOSAGE
There is no known antidote for TAXOL overdosage. [illegible] of overdosage would consist of bone marrow [illegible] mucositis.

HOW SUPPLIED
NDC 0015-3475-30 30 mg/5 mL multidose [illegible]
NDC 0015-3476-30 100 mg/16.7 mL multidose [illegible]
U.S. Patent Nos. 5,496,804 and 5,641,803.
Storage: Store the vials in original cartons between [illegible] original package to protect from light.

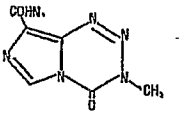
Mead Johnson
ONCOLOGY [illegible]
[illegible]

K4-B001-3-58
006186-02

ONCOLOGY THERAPEUTICS NETWORK
1-800-482-6700

TEMODAR™
(temozolomide) CAPSULES

DESCRIPTION
TEMODAR Capsules for oral administration contain temozolomide, an imida-zotetrazine derivative. The chemical name of temozolomide is 3,4-dihydro-3-methyl-4-oxoimidazo[5,1-d]-as-tetrazine-8-carboxamide. The structural formula is:



The material is a white to light tan/light pink powder with a molecular formula of $C_6H_6N_8O_2$ and a molecular weight of 194.15. The molecule is stable at acidic pH (<5), and labile at pH >7, hence can be administered orally. The prodrug, temozolomide, is rapidly hydrolysed to the active 5-(3-methyltriazen-1-yl)imidazole-4-carboxamide (MTIC) at neutral and alkaline pH values, with hydrolysis taking place even faster at alkaline pH.
Each capsule contains either 5 mg, 20 mg, 100 mg, or 250 mg of temozolomide. The inactive ingredients for TEMODAR Capsules are lactose anhydrous, colloidal silicon dioxide, sodium starch glycolate, tartaric acid, and stearic acid. Gelatin capsule shells contain titanium dioxide. The capsules are imprinted with pharmaceutical ink.

TEMODAR 5 mg: green imprint contains pharmaceutical grade shellac, anhydrous ethyl alcohol, isopropyl alcohol, n-butyl alcohol, propylene glycol, ammonium hydroxide, titanium dioxide, yellow iron oxide, and FD&C Blue #2 aluminum lake.

TEMODAR 20 mg: brown imprint also contains pharmaceutical grade shellac, anhydrous ethyl alcohol, isopropyl alcohol, n-butyl alcohol, propylene glycol, purified water, ammonium hydroxide, potassium hydroxide, titanium dioxide, black iron oxide, yellow iron oxide, brown iron oxide, and red iron oxide.

TEMODAR 100 mg: blue imprint contains pharmaceutical glaze (modified) in an ethanol/shellac mixture, isopropyl alcohol, n-butyl alcohol, propylene glycol, titanium dioxide, and FD & C Blue #2 aluminum lake.

TEMODAR250mg: black, imprint contains pharmaceutical grade shellac, anhydrous ethyl alcohol, isopropyl alcohol, n-butyl alcohol, propylene glycol, purified water, ammonium hydroxide, potassium hydroxide, and black iron oxide.

CLINICAL PHARMACOLOGY
Mechanism of Action: Temozolomide is not directly active but undergoes rapid nonenzymatic conversion at physiologic pH to the reactive compound MTIC. The cytotoxicity of MTIC is thought to be primarily due to alkylation of DNA. Alkylation (methylation) occurs mainly at the O^6 and N^7 positions of guanine.
Pharmacokinetics: Temozolomide is rapidly and completely absorbed after oral administration; peak plasma concentration occurs in 1 hour. Food reduces the rate and extent of temozolomide absorption. Mean peak plasma concentration and AUC decreased by 32% and 9%, respectively, and Tmax increased 2-fold (from 1.1 to 2.25 hours) when temozolomide was administered after a modified high-fat breakfast. Temozolomide is rapidly eliminated with a mean elimination half-life of 1.8 hours and exhibits linear kinetics over the therapeutic dosing range. Temozolomide has a mean apparent volume of distribution of 0.4 L/kg (%CV=13%). It is weakly bound to human plasma proteins; the mean percent bound of drug-related total radioactivity is 15%.
Metabolism and Elimination: Temozolomide is spontaneously hydrolyzed at physiologic pH to the active species, 3-methyl-(triazen-1-yl)imidazole-4-car-boxamide (MTIC) and to temozolomide acid metabolite. MTIC is further hydrolyzed to 5-amino-imidazole-4-carboxamide (AIC) which is known to be an intermediate in purine and nucleic acid biosynthesis and to methylhydrazine, which is believed to be the active alkylating species. Cytochrome P450 enzymes play only a minor role in the metabolism of temozolomide and MTIC. Relative to the AUC of temozolomide, the exposure to MTIC and AIC is 2.4% and 23%, respectively. About 38% of the administered temozolomide total radioactive dose is recovered over 7 days; 37.7% in urine and 0.8% in feces. The majority of the recovery of radioactivity in urine is as unchanged temozolomide (5.6%), AIC (12%), temozolomide acid metabolite (2.3%), and unidentified polar metabolite(s) (17%). Overall clearance of temozolomide is about 5.5 L/hr/m².
Special Populations: Age Population pharmacokinetic analysis indicates that age (range 19 to 78 years) has no influence on the pharmacokinetics of temo-zolomide. In the anaplastic astrocytoma study population, patients 70 years of age or older had a higher incidence of Grade 4 neutropenia and Grade 4 thrombocytopenia in the first cycle of therapy than patients under 70 years of age (see **PRECAUTIONS**). In the entire safety database, however, there did not appear to be a higher incidence in patients 70 years of age or older (see **ADVERSE REACTIONS**).
Gender Population pharmacokinetic analysis indicates that women have an approximately 5% lower clearance (adjusted for body surface area) for temo-zolomide than men. Women have higher incidences of Grade 4 neutropenia and thrombocytopenia in the first cycle of therapy than men (see **ADVERSE REACTIONS**).
Race The effect of race on the pharmacokinetics of temozolomide has not been studied.
Tobacco Use Population pharmacokinetic analysis indicates that the oral clearance of temozolomide is similar in smokers and nonsmokers.
Creatinine Clearance Population pharmacokinetic analysis indicates that creatinine clearance over the range of 36-130 mL/min/m² has no effect on the clearance of temozolomide after oral administration. The pharmacokinetics of temozolomide have not been studied in patients with severely impaired renal function (CLcr<36mL/min/m²). Caution should be exercised when TEMODAR is administered to patients with severe renal impairment. TEMODAR has not been studied in patients on dialysis.
Hepatically Impaired Patients In a pharmacokinetic study, the pharmacokinetics of temozolomide in patients with mild-to-moderate hepatic impairment (Child's-Pugh Class I-II) were similar to those observed in patients with normal hepatic function. Caution should be exercised when temozolomide is administered to patients with severe hepatic impairment.
Pediatrics Pediatric patients (3 to 17 years of age) and adult patients have similar clearance and half-life values for temozolomide. There is no clinical experience with the use of TEMODAR in children under the age of 3 years.
Drug-Drug Interactions In a multiple-dose study, administration of TEMODAR with ranitidine did not change the C_{max} or AUC values for temozolomide or MTIC.
Population analysis indicates that administration of valproic acid decreases the clearance of temozolomide by about 5% (see **PRECAUTIONS**).
Population analysis failed to demonstrate any influence of coadministered dexamethasone, prochlorperazine, phenytoin, carbamazepine, ondansetron, H_2-receptor antagonists, or phenobarbital on the clearance of orally administered temozolomide.
Clinical Studies A single-arm, multicenter study was conducted in 162 patients who had anaplastic astrocytoma at first relapse and who had a baseline Karnofsky performance status of 70 or greater. Patients had previously received radiation therapy and may also have previously received a nitrosourea with or without other chemotherapy. Fifty-four patients had disease progression on prior therapy with both a nitrosourea and procarbazine and their malignancy was considered refractory to chemotherapy (refractory anaplastic astrocytoma population). Median age of this subgroup of 54 patients was 42 years (19 to 76). Sixty-five percent were male. Seventy-two percent of patients had a KPS of ≥80. Sixty-three percent of patients had surgery other than a biopsy at the time of initial diagnosis. Of those patients undergoing resection, 73% underwent a subtotal resection and 27% underwent a gross total resection. Eighteen percent of patients had surgery at the time of first relapse. The median time from initial diagnosis to first relapse was 13.8 months (4.2 to 75.4).
TEMODAR was given for the first 5 consecutive days of a 28-day cycle at a starting dose of 150 mg/m²/day. If the nadir and day of dosing (Day 29, Day 1 of next cycle) absolute neutrophil count was ≥1.5 x 10^9/L (1,500/μL) and the nadir and Day 29, Day 1 of next cycle, platelet count was ≥100 x 10^9/L (100,000/μL), the TEMODAR dose was increased to 200 mg/m²/day for the first 5 consecutive days of a 28-day cycle.
In the refractory anaplastic astrocytoma population the overall tumor response rate (CR+ PR) was 22% (12/54 patients) and the complete response rate was 9% (5/54 patients). The median duration of all responses was 50 weeks (range of 16 to 114 weeks) and the median duration of complete responses was 64 weeks (range of 52 to 114 weeks). In this population, progression-free survival at 6 months was 45% (95% confidence interval 31% to 58%) and progression-free survival at 12 months was 23% (95% confidence interval 16% to 42%). Median progression-free survival was 4.4 months. Overall survival at 6 months was 74% (95% confidence interval 62% to 86%) and 12-month overall survival was 65% (95% confidence interval 52% to 78%). Median overall survival was 15.9 months.

INDICATIONS AND USAGE
TEMODAR (temozolomide) Capsules are indicated for the treatment of adult patients with refractory anaplastic astrocytoma, i.e., patients at first relapse who have experienced disease progression on a drug regimen containing a nitrosourea and procarbazine.
This indication is based on the response rate in the indicated population. No results are available from randomized controlled trials in recurrent anaplastic astrocytoma that demonstrate a clinical benefit resulting from treatment, such as improvement in disease-related symptoms, delayed disease progression, or improved survival.

CONTRAINDICATIONS
TEMODAR (temozolomide) Capsules are contraindicated in patients who have a history of hypersensitivity reaction to any of its components. TEMODAR is also contraindicated in patients who have a history of hypersensitivity to DTIC, since both drugs are metabolized to MTIC.

WARNINGS
Patients treated with TEMODAR may experience myelosuppression. Prior to dosing, patients must have an absolute neutrophil count (ANC) ≥1.5 x 10^9/L and a platelet count ≥100 x 10^9/L. A complete blood count should be obtained on Day 22 (21 days after the first dose) or within 48 hours of that day, and weekly until the ANC is above 1.5 x 10^9/L and platelet count exceeds 100 x 10^9/L. In the clinical trials, if the ANC fell to <1.0 x 10^9/L or the platelet count was <50 x 10^9/L during any cycle, the next cycle was reduced by 50 mg/m², but not below 100 mg/m². Patients who do not tolerate 100 mg/m² should not receive TEMODAR. Geriatric patients and women have been shown in clinical trials to have a higher risk of developing myelosuppression. Myelosuppression generally occurred late in the treatment cycle. The median nadirs occurred at 26 days for platelets (range 21 to 40 days) and 28 days for neutrophils (range 1 to 44 days). Only 14% (22/158) of patients had a neutrophil nadir and 20% (32/158) of patients had a platelet nadir which may have delayed the start of the next cycle. Neutrophil and platelet counts returned to normal, on average, within 14 days of nadir counts (see **PRECAUTIONS**).
Pregnancy: Temozolomide may cause fetal harm when administered to a pregnant woman. Five consecutive days of oral administration of 75 mg/m²/day in rats and 150 mg/m²/day in rabbits during the period of organogenesis (3/8 and 3/4 the maximum recommended human dose, respectively) caused numerous malformations of the external organs, soft tissues, and skeleton in both species. Doses of 150mg/m²/day in rats and rabbits also caused embryolethality as indicated by increased resorptions. There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant during therapy with TEMODAR.

PRECAUTIONS
Information for Patients: In clinical trials, the most frequently occurring adverse effects were nausea and vomiting. These were usually either self-limiting or readily controlled with standard antiemetic therapy. Capsules should not be opened. If capsules are accidentally opened or damaged, rigorous precautions should be taken with the capsule contents to avoid inhalation or contact with the skin or mucous membranes. The medication should be kept away from children and pets.
Drug Interaction: Administration of valproic acid decreases oral clearance of temozolomide by about 5%. The clinical implication of this effect is not known.
Patients with Severe Hepatic or Renal Impairment: Caution should be exercised when TEMODAR is administered to patients with severe hepatic or renal impairment (see Special Populations).
Geriatrics: Clinical studies of temozolomide did not include sufficient numbers of subjects aged 65 and over to determine whether they responded differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. Caution should be exercised when treating elderly patients.
In the anaplastic astrocytoma study population, patients 70 years of age or older had a higher incidence of Grade 4 neutropenia and Grade 4 thrombocytopenia (2/8; 25%, p=.31 and 2/10; 20%, p=.09, respectively) in the first cycle of therapy than patients under 70 years of age (see **ADVERSE REACTIONS**).
Laboratory Tests: A complete blood count should be obtained on Day 22 (21 days after the first dose). Blood counts should be performed weekly until recovery if the ANC falls below 1.5x10^9/L and the platelet count falls below 100x10^9/L.
Carcinogenesis, Mutagenesis, and Impairment of Fertility: Standard carcinogenicity studies were not conducted with temozolomide. In rats treated with 200 mg/m² temozolomide (equivalent to the maximum recommended daily human dose) on 5 consecutive days every 28 days for 3 cycles, mammary carcinomas were found in both males and females. With 6 cycles of treatment at 25, 50, and 125 mg/m² (about 1/8 to 1/2 the maximum recommended daily human dose), mammary carcinomas were observed at all doses and fibrosarcomas of the heart, eye, seminal vesicles, salivary glands, abdominal cavity, uterus, and prostate; carcinoma of the seminal vesicles, schwannoma of the heart, optic nerve, and harderian gland; and adenomas of the skin, lung, pituitary, and thyroid were observed at the high dose.
Temozolomide was mutagenic *in vitro* in bacteria (Ames assay) and clastogenic in mammalian cells (human peripheral blood lymphocyte assays).
Reproductive function studies have not been conducted with temozolomide. However, multicycle toxicology studies in rats and dogs have demonstrated testicular toxicity (syncytial cells/immature sperm, testicular atrophy) at doses of 50 mg/m² in rats and 125 mg/m² in dogs (1/4 and 5/8, respectively, of the maximum recommended human dose on a body surface area basis).
Pregnancy Category D: See **WARNINGS** section.
Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from TEMODAR, patients receiving TEMODAR should discontinue nursing.
Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS
Tables 1 and 2 show the incidence of adverse events in the 158 patients in the anaplastic astrocytoma study for whom data are available. In the absence of a control group, it is not clear in many cases whether these events should be attributed to temozolomide or the patients' underlying conditions, but nausea, vomiting, fatigue, and hematologic effects appear to be clearly drug related. The most frequently occurring side effects were nausea, vomiting, headache, and fatigue. The adverse events were usually NCI Common Toxicity Criteria (CTC) Grade 1 or 2 (mild to moderate in severity) and were self-limiting, with nausea and vomiting readily controlled with antiemetics. The incidence of severe nausea and vomiting (CTC Grade 3 or 4) was 10% and 6%, respectively.
Myelosuppression (thrombocytopenia and neutropenia) was the dose-limiting adverse event. It usually occurred within the first few cycles of therapy and was not cumulative. Myelosuppression occurred late in the treatment cycle and returned to normal, on average, within 14 days of nadir counts. The median nadirs occurred at 26 days for platelets (range 21 to 40 days) and 28 days for neutrophils (range 1 to 44 days). Only 14% (22/158) of patients had a neutrophil nadir and 20% (32/158) of patients had a platelet nadir which may have delayed the start of the next cycle (see **WARNINGS**). Less than 10% of patients required hospitalization, blood transfusion, or discontinuation of therapy due to myelosuppression.
In clinical trial experience with 110 to 111 women and 169 to 174 men (depending on measurements), there were higher rates of Grade 4 neutropenia (ANC < 500 cells/μL) and thrombocytopenia (< 20,000 cells/μL) in women than men in the first cycle of therapy: (12% versus 5% and 9% versus 3%, respectively). In the entire safety database for which hematologic data exist (N=932), 7% (4/61) and 9.5% (6/63) of patients over age 70 experienced Grade 4 neutropenia or thrombocytopenia in the first cycle, respectively. For patients less than or equal to age 70, 7% (62/871) and 5.5% (48/879) experienced Grade 4 neutropenia or thrombocytopenia in the first cycle, respectively.

Table 1
Adverse Events in the Anaplastic Astrocytoma Trial (≥5%)

	No. (%) of TEMODAR Patients (N=158)	
	All Events	Grade 3/4
Any Adverse Event	153 (97)	79 (50)
Body as a Whole		
Headache	65 (41)	10 (6)
Fatigue	54 (34)	7 (4)
Asthenia	20 (13)	9 (6)
Fever	21 (13)	3 (2)
Back pain	12 (8)	4 (3)
Cardiovascular		
Edema peripheral	17 (11)	1 (1)
Central and Peripheral Nervous System		
Convulsions	36 (23)	8 (5)
Hemiparesis	29 (18)	10 (6)
Dizziness	19 (12)	1 (1)
Coordination abnormal	17 (11)	2 (1)
Amnesia	16 (10)	6 (4)
Insomnia	16 (10)	0
Paresthesia	15 (9)	1 (1)
Somnolence	15 (9)	5 (3)
Paresis	13 (8)	4 (3)
Urinary incontinence	13 (8)	3 (2)
Ataxia	12 (8)	3 (2)
Dysphasia	11 (7)	1 (1)
Convulsions focal	9 (6)	0
Gait abnormal	9 (6)	1 (1)
Confusion	8 (5)	0
Endocrine		
Adrenal hypercorticism	13 (8)	0
Gastrointestinal System		
Nausea	84 (53)	16 (10)
Vomiting	66 (42)	10 (6)
Constipation	52 (33)	1 (1)
Diarrhea	25 (16)	3 (2)
Abdominal pain	14 (9)	2 (1)
Anorexia	14 (9)	1 (1)
Metabolic		
Weight increase	8 (5)	0
Musculoskeletal System		
Myalgia	8 (5)	
Psychiatric Disorders		
Anxiety	11 (7)	1 (1)
Depression	10 (6)	0
Reproductive Disorders		
Breast pain, female	4 (6)	
Resistance Mechanism Disorders		
Infection viral	17 (11)	0
Respiratory System		
Upper respiratory tract infection	13 (8)	0
Pharyngitis	12 (8)	0
Sinusitis	10 (6)	0
Coughing	8 (5)	0
Skin and Appendages		
Rash	13 (8)	0
Pruritus	12 (8)	2 (1)
Urinary System		
Urinary tract infection	12 (8)	0
Micturition increased frequency	9 (6)	0
Vision		
Diplopia	8 (5)	0
Vision Abnormal*	8 (5)	

*Blurred vision, visual deficit, vision changes, vision troubles.

Table 2
Adverse Hematologic Effects (Grade 3 to 4) in the Anaplastic Astrocytoma Trial

	TEMODAR*	
Hemoglobin	7/158	(4%)
Neutrophils	20/142	(14%)
Platelets	29/156	(19%)
WBC	18/158	(11%)

*Change from Grade 0 to 2 at baseline to Grade 3 or 4 during treatment.

OVERDOSAGE

Doses of 600, 750, 1,000, and 1,250 mg/m² (total dose per cycle over 5 days) have been evaluated clinically in patients. Dose-limiting toxicity was hematologic and was reported at 1,000 mg/m² and at 1,250 mg/m². Up to 1,000 mg/m² has been taken as a single dose, with only the expected effects of neutropenia and thrombocytopenia resulting. In the event of an over-dose, hematologic evaluation is needed. Supportive measures should be provided as necessary.

DOSAGE AND ADMINISTRATION

Dosage of TEMODAR must be adjusted according to nadir neutrophil and platelet counts in the previous cycle and neutrophil and platelet counts at the time of initiating the next cycle. The initial dose is 150 mg/m² orally once daily for 5 consecutive days per 28-day treatment cycle. If both the nadir and day of dosing (Day 29, Day 1 of next cycle) absolute neutrophil counts (ANC) are ≥1.5 x 10^9/L (1,500/μL) and both the nadir and Day 29, Day 1 of next cycle platelet counts are ≥100 x 10^9/L (100,000/μL), the TEMODAR dose may be increased to 200 mg/m²/day for 5 consecutive days per 28-day treatment cycle. During treatment, a complete blood count should be obtained on Day 22 (21 days after the first dose) or within 48 hours of that day, and weekly until the ANC is above 1.5 x 10^9/L (1,500/μL) and the platelet count exceeds 100 x 10^9/L (100,000/μL). The next cycle of TEMODAR should not be started until the ANC and platelet count exceed these levels. If the ANC falls to <1.0 x 10^9/L (1,000/μL) or the platelet count is <50 x 10^9/L (50,000/μL) during any cycle, the next cycle should be reduced by 50 mg/m², but not below 100 mg/m², the lowest recommended dose (see Table 3) (see WARNINGS).

TEMODAR therapy can be continued until disease progression. In the clinical trial, treatment could be continued for a maximum of 2 years; but the optimum duration of therapy is not known. For TEMODAR dosage calculations based on body surface area (BSA), see Table 4. For suggested capsule combinations based on daily dose, see Table 5.

Table 3 Dosing Modification Table

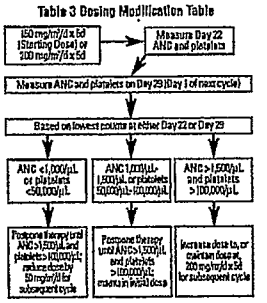


Table 4
Daily Dose Calculations by Body Surface Area (BSA) for 5 consecutive days per 28-day treatment cycle for the initial chemotherapy cycle (150 mg/m²) and for subsequent chemotherapy cycles (200 mg/m²) for patients whose nadir and day of dosing (Day 29, Day 1 of next cycle) absolute neutrophil count (ANC) is >1.5 x 10^9/L (1,500/μL) and whose nadir and Day 29, Day 1 of next cycle platelet count is >100 x 10^9/L (100,000/μL).

Total BSA (m²)	150 mg/m² (mg daily)	200 mg/m² (mg daily)
0.5	75	100
0.6	90	120
0.7	105	140
0.8	120	160
0.9	135	180
1.0	150	200
1.1	165	220
1.2	180	240
1.3	195	260
1.4	210	280
1.5	225	300
1.6	240	320
1.7	255	340
1.8	270	360
1.9	285	380
2.0	300	400
2.1	315	420
2.2	330	440
2.3	345	460
2.4	360	480
2.5	375	500

Table 5
Suggested Capsule Combinations Based on Daily Dose

Number of Daily Capsules by Strength (mg)				
Total Daily Dose (mg)	250	100	20	5
200	0	2	0	0
205	0	2	0	1
210	0	2	0	2
215	0	2	0	3
220	0	2	1	0
225	0	2	1	1
230	0	2	1	2
235	0	2	1	3
240	0	2	2	0
245	0	2	2	1
250	1	0	0	0
255	1	0	0	1
260	1	0	0	2
265	1	0	0	3
270	1	0	1	0
275	1	0	1	1
280	1	0	1	2
285	1	0	1	3
290	1	0	2	0
295	1	0	2	1
300	0	3	0	0
305	0	3	0	1
310	0	3	0	2
315	0	3	0	3
320	0	3	1	0
325	0	3	1	1
330	1	0	4	0
335	1	0	4	1
340	0	3	2	0
345	0	3	2	1
350	1	1	0	0
355	1	1	0	1
360	1	1	0	2
365	1	1	0	3
370	1	1	1	0
375	1	1	1	1
380	1	1	1	2
385	1	1	1	3
390	1	1	2	0
395	1	1	2	1
400	0	4	0	0
405	0	4	0	1
410	0	4	0	2
415	0	4	0	3
420	0	4	1	0
425	0	4	1	1
430	1	1	4	0

Table 5 *continued*
Suggested Capsule Combinations Based on Daily Dose

Number of Daily Capsules by Strength (mg)				
Total Daily Dose (mg)	250	100	20	5
435	0	4	1	3
440	0	4	2	0
445	0	4	2	1
450	1	2	0	0
455	1	2	0	1
460	1	2	0	2
465	1	2	0	3
470	1	2	1	0
475	1	2	1	1
480	1	2	1	2
485	1	2	1	3
490	1	2	2	0
495	1	2	2	1
500	2	0	0	0

In the clinical trial, TEMODAR was administered under both fasting and nonfasting conditions; however, absorption is affected by food (see CLINICAL PHARMACOLOGY) and consistency of administration with respect to food is recommended. There are no dietary restrictions with temozolomide. To reduce nausea and vomiting, temozolomide should be taken on an empty stomach. Bedtime administration may be advised. Antiemetic therapy may be administered prior to and/or following administration of TEMODAR.

TEMODAR (temozolomide) Capsules should not be opened or chewed. They should be swallowed whole with a glass of water.

Handling and Disposal: Temozolomide causes the rapid appearance of malignant tumors in rats. Capsules should not be opened. If capsules are accidentally opened or damaged, rigorous precautions should be taken with the capsule contents to avoid inhalation or contact with the skin or mucous membranes. Procedures for proper handling and disposal of anticancer drugs should be considered.[1-7] Several guidelines on this subject have been published. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

HOW SUPPLIED

TEMODAR (temozolomide) Capsules are supplied in amber glass bottles with child-resistant polypropylene caps containing the following capsule strengths:

TEMODAR (temozolomide) Capsules 5 mg: 5 and 20 capsule bottles.
- 5 count - NDC 0085-1248-01
- 20 count - NDC 0085-1248-02

TEMODAR (temozolomide) Capsules 20 mg: 5 and 20 capsule bottles.
- 5 count - NDC 0085-1244-01
- 20 count - NDC 0085-1244-02

TEMODAR (temozolomide) Capsules 100 mg: 5 and 20 capsule bottles.
- 5 count - NDC 0085-1259-01
- 20 count - NDC 0085-1259-02

TEMODAR (temozolomide) Capsules 250 mg: 5 and 20 capsule bottles.
- 5 count - NDC 0085-1252-01
- 20 count - NDC 0085-1252-02

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F).
[See USP Controlled Room Temperature]

REFERENCES

1. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs, NIH Publication No. 83-2621. For sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20402.
2. AMA Council Report. Guidelines for Handling Parenteral Antineoplastics. *JAMA*. 1985;2.53(11):1590-1592.
3. National Study Commission on Cytotoxic Exposure - Recommendations for Handling Cytotoxic Agents. Available from Louis P. Jeffrey, ScD., Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, Massachusetts 02115.
4. Clinical Oncological Society of Australia, Guidelines and Recommendations for Safe Handling of Antineoplastic Agents. *Med J Australia*. 1983;1:426-428.
5. Jones RB, et al. Safe Handling Of Chemotherapeutic Agents: A Report from the Mount Sinai Medical Center. CA - *A Cancer Journal for Clinicians*. 1983;(Sept/Oct):258-263.
6. American Society of Hospital Pharmacists Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs. Am J Hosp Pharm. 1990;47:1033-1049.
7. Controlling Occupational Exposure to Hazardous Drugs. (OSHA Work-Practice Guidelines), *Am J Health-Syst Pharm*. 1996; 53: 1669-1685.

Schering Corporation
Kenilworth, NJ 07033 USA

8/99 B-22487809

℞ ONLY

VePesid®
(etoposide)

Injection and Capsules

...d Prescribing Information, 9/98. For complete ...mation, please consult official package circular.

...eid be administered under the supervision of a ...ician experienced in the use of cancer ...otic agents. Severe myelosuppression with ...ction or bleeding may occur.

...S AND USAGE

...poside) is indicated in the management of the ...ing:

...y Testicular Tumors: VePesid For Injection in ...bination therapy with other approved chemotherapeutic ...s with refractory testicular tumors who have ...ved appropriate surgical, chemotherapeutic, and ...otherapy.

...ation on the use of VePesid Capsules in the treatment ...ancer are not available.

...Cell Lung Cancer: VePesid For Injection and/or ...bination with other approved chemotherapeutic ...s as first line treatment in patients with small cell lung ...

...INDICATIONS

...s contraindicated in patients who have demonstrated a ...ersensitivity to etoposide or any component of the ...

...ts treated with VePesid must be frequently observed ...pression both during and after therapy. ...ns resulting in death has been reported. Dose-...marrow suppression is the most significant toxicity ...with VePesid therapy. Therefore, the following studies ...ormed at the start of therapy and prior to each ...ose of VePesid: platelet count, hemoglobin, white ...unt, and differential. The occurrence of a platelet ...count <100,000/mm³ or an absolute neutrophil count below ...2,000/mm³ is an indication to withhold further therapy until the ...ts have sufficiently recovered.

...ients should be aware of the possible occurrence of an ...ic reaction manifested by chills, fever, tachycardia, ...ospasm, dyspnea, and hypotension. Higher rates of ...ypotensive reactions have been reported in children who ...ved dosages at concentrations higher than those ...ended. The role that concentration of infusion (or rate of ...ion) in the development of anaphylactic-like reactions is ...wn. (See ADVERSE REACTIONS section.) Treatment is ...ic. The infusion should be terminated immediately, ...ould include the administration of pressor agents, corticosteroids, ...ne, and/or volume expanders at the discretion of the ...

...For intravenous administration, VePesid should be given only by ...ntravenous infusion (usually over a 30 to 60 minute period) ...ension has been reported as a possible side effect of ...id injection.

...ancy: VePesid can cause fetal harm when administered ...o a pregnant woman. Etoposide has been shown to be teratogenic ...

...ntravenous etoposide dose of 0.4 mg/kg/day (about ...the human dose on a mg/m² basis) during ...caused maternal toxicity, embryotoxicity, and ...(skeletal abnormalities, exencephaly, ...and anophthalmia); higher doses of 1.2 and 3.6 ...1/7th and 1/2 of human dose on a mg/m² basis) ...and 100% embryonic resorptions. In mice, a single ...16th of human dose on a mg/m² basis) dose of ...nistered intraperitoneally on days 6, 7, 8 of ...l embryotoxicity, cranial abnormalities, and major ...ations. An I.P. dose of 1.5 mg/kg (about 1/10th of ...a mg/m² basis) on day 7 of gestation caused an ...incidence of intrauterine death and fetal ...and a significant decrease in the average fetal body ...

...Childbearing potential should be advised to avoid ...ancy. If this drug is used during pregnancy, or if the ...ent becomes pregnant while receiving this drug, the patient ...ld of the potential hazard to the fetus.

...etoposide should be considered a potential carcinogen in ...humans. Occurrence of acute leukemia with or without a ...period has been reported in rare instances in patients ...ated with etoposide alone or in association with other ...ancers. The risk of development of a preleukemic or ...ic state is unclear. Carcinogenicity tests with VePesid ...have not been conducted in laboratory animals.

...TIONS

...In those instances where the use of VePesid is considered ...ssary, the physician must evaluate the need and ...ility of the drug against the risk of adverse reactions. Most ...adverse reactions are reversible if detected early. If severe ...occur, the drug should be reduced in dosage or ...ed, and appropriate corrective measures should be ...n according to the clinical judgment of the physician. ...ent of VePesid therapy should be carried out with ...ful and adequate consideration of the further need for ...py as well as possible recurrence of toxicity.

...Patients with low serum albumin may be at an increased risk ...severe related toxicities.

...ratory Tests: Periodic complete blood counts should be ...ed in the course of VePesid treatment. They should be ...ed prior to each cycle of therapy and at appropriate ...ls during and after therapy. At least one determination ...ld be made prior to each dose of VePesid.

Renal Impairment: In patients with impaired renal function, the following initial dose modification should be considered based on measured creatinine clearance:

Measured Creatinine Clearance	> 50 mL/min	15-50 mL/min
etoposide	100% of dose	75% of dose

Subsequent VePesid (etoposide) dosing should be based on patient tolerance and clinical effect.

Data are not available in patients with creatinine clearances <15 mL/min and further dose reduction should be considered in these patients.

Carcinogenesis, (see WARNINGS section) Mutagenesis, Impairment of Fertility: Etoposide has been shown to be mutagenic in Ames assay.

Treatment of Swiss-Albino mice with 1.5 mg/kg I.P. of VePesid on day 7 of gestation increased the incidence of intrauterine death and fetal malformations as well as significantly decreased the average fetal body weight. Maternal weight gain was not affected.

Irreversible testicular atrophy was present in rats treated with etoposide intravenously for 30 days at 0.5 mg/kg/day (about 1/16th of the human dose on a mg/m² basis).

Pregnancy: Pregnancy "Category D". (See WARNINGS section.)

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from VePesid, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

VePesid For Injection contains polysorbate 80. In premature infants, a life-threatening syndrome consisting of liver and renal failure, pulmonary deterioration, thrombocytopenia, and ascites has been associated with an injectable vitamin E product containing polysorbate 80. Anaphylactic reactions have been reported in pediatric patients. (See WARNINGS section.)

Drug Interactions: High-dose cyclosporine resulting in concentrations above 2000 ng/mL administered with oral etoposide has led to an 80% increase in etoposide exposure with a 38% decrease in total body clearance of etoposide compared to etoposide alone.

ADVERSE REACTIONS

The following data on adverse reactions are based on both oral and intravenous administration of VePesid as a single agent, using several different dose schedules for treatment of a wide variety of malignancies.

Hematologic Toxicity: Myelosuppression is dose related and dose limiting, with granulocyte nadirs occurring 7 to 14 days after drug administration and platelet nadirs occurring 9 to 16 days after drug administration. Bone marrow recovery is usually complete by day 20, and no cumulative toxicity has been reported. Fever and infection have also been reported in patients with neutropenia. Death associated with myelosuppression has been reported.

The occurrence of acute leukemia with or without a preleukemic phase has been reported rarely in patients treated with VePesid in association with other antineoplastic agents. (See WARNINGS section.)

Gastrointestinal Toxicity: Nausea and vomiting are the major gastrointestinal toxicities. The severity of such nausea and vomiting is generally mild to moderate with treatment discontinuation required in 1% of patients. Nausea and vomiting can usually be controlled with standard antiemetic therapy. Mild to severe mucositis/esophagitis may occur. Gastrointestinal toxicities are slightly more frequent after oral administration than after intravenous infusion.

Hypotension: Transient hypotension following rapid intravenous administration has been reported in 1% to 2% of patients. It has not been associated with cardiac toxicity or electrocardiographic changes. No delayed hypotension has been noted. To prevent this rare occurrence, it is recommended that VePesid be administered by slow intravenous infusion over a 30- to 60-minute period. If hypotension occurs, it usually responds to cessation of the infusion and administration of fluids or other supportive therapy as appropriate. When restarting the infusion, a slower administration rate should be used.

Allergic Reactions: Anaphylactic-like reactions characterized by chills, fever, tachycardia, bronchospasm, dyspnea, and/or hypotension have been reported to occur in 0.7% to 2% of patients receiving intravenous VePesid and in less than 1% of the patients treated with the oral capsules. These reactions have usually responded promptly to the cessation of the infusion and administration of pressor agents, corticosteroids, antihistamines, or volume expanders as appropriate; however, the reactions can be fatal. Hypertension and/or flushing have also been reported. Blood pressure usually normalizes within a few hours after cessation of the infusion. Anaphylactic-like reactions have occurred during the initial infusion of VePesid.

Facial/tongue swelling, coughing, diaphoresis, cyanosis, tightness in throat, laryngospasm, back pain, and/or loss of consciousness have sometimes occurred in association with the above reactions. In addition, an apparent hypersensitivity-associated apnea has been reported rarely.

Rash, urticaria, and/or pruritus have infrequently been reported at recommended doses. At investigational doses, a generalized pruritic erythematous maculopapular rash, consistent with perivasculitis, has been reported.

Alopecia: Reversible alopecia, sometimes progressing to total baldness, was observed in up to 66% of patients.

Other Toxicities: The following adverse reactions have been infrequently reported: abdominal pain, aftertaste, constipation, dysphagia, asthenia, fatigue, malaise, somnolence, transient cortical blindness, optic neuritis, interstitial pneumonitis/pulmonary fibrosis, fever, seizure (occasionally associated with allergic reactions), Stevens-Johnson syndrome, and toxic epidermal necrolysis, pigmentation, and a single report of radiation recall dermatitis.

Hepatic toxicity, generally in patients receiving higher doses of the drug than those recommended, has been reported with VePesid. Metabolic acidosis has also been reported in patients receiving higher doses.

Reports of extravasation with swelling have been received post-marketing. Rarely extravasation has been associated with necrosis and venous induration.

The incidences of adverse reactions in the table that follows are derived from multiple data bases from studies in 2,081 patients when VePesid was used either orally or by injection as a single agent.

ADVERSE DRUG EFFECT	PERCENT RANGE OF REPORTED INCIDENCE
Hematologic toxicity	
Leukopenia (less than 1,000 WBC/mm³)	3-17
Leukopenia (less than 4,000 WBC/mm³)	60-91
Thrombocytopenia (less than 50,000 platelets/mm³)	1-20
Thrombocytopenia (less than 100,000 platelets/mm³)	22-41
Anemia	0-33
Gastrointestinal toxicity	
Nausea and vomiting	31-43
Abdominal pain	0-2
Anorexia	10-13
Diarrhea	1-13
Stomatitis	1-6
Hepatic	0-3
Alopecia	8-66
Peripheral neurotoxicity	1-2
Hypotension	1-2
Allergic reaction	1-2

OVERDOSAGE

No proven antidotes have been established for VePesid (etoposide) overdosage.

DOSAGE AND ADMINISTRATION

Note: Plastic devices made of acrylic or ABS (a polymer composed of acrylonitrile, butadiene, and styrene) have been reported to crack and leak when used with undiluted VePesid For Injection.

VePesid For Injection: The usual dose of VePesid For Injection in testicular cancer in combination with other approved chemotherapeutic agents ranges from 50 to 100 mg/m²/day on days 1 through 5 to 100 mg/m²/day on days 1, 3, and 5.

In small cell lung cancer, the VePesid For Injection dose in combination with other approved chemotherapeutic drugs ranges from 35 mg/m²/day for 4 days to 50 mg/m²/day for 5 days.

For recommended dosing adjustments in patients with renal impairment, see PRECAUTIONS section.

Chemotherapy courses are repeated at 3- to 4-week intervals after adequate recovery from any toxicity.

VePesid Capsules: In small cell lung cancer, the recommended dose of VePesid Capsules is two times the I.V. dose rounded to the nearest 50 mg.

The dosage, by either route, should be modified to take into account the myelosuppressive effects of other drugs in the combination or the effects of prior x-ray therapy or chemotherapy which may have compromised bone marrow reserve.

Administration Precautions: As with other potentially toxic compounds, caution should be exercised in handling and preparing the solution of VePesid. Skin reactions associated with accidental exposure to VePesid may occur. The use of gloves is recommended. If VePesid solution contacts the skin or mucosa, immediately and thoroughly wash the skin with soap and water and flush the mucosa with water.

Preparation for Intravenous Administration: VePesid For Injection must be diluted prior to use with either 5% Dextrose Injection, USP or 0.9% Sodium Chloride Injection, USP, to give a final concentration of 0.2 to 0.4 mg/mL. If solutions are prepared at concentrations above 0.4 mg/mL, precipitation may occur. Hypotension following rapid intravenous administration has been reported, hence, it is recommended that the VePesid solution be administered over a 30- to 60-minute period. A longer duration of administration may be used if the volume of fluid to be infused is a concern. VePesid should not be given by rapid intravenous injection.

Parenteral drug products should be inspected visually for particulate matter and discoloration (see DESCRIPTION section) prior to administration whenever solution and container permit.

Stability: Undiluted vials of VePesid For Injection are stable for 24 months at room temperature (25°C). Vials diluted as recommended to a concentration of 0.2 or 0.4 mg/mL are stable for 96 and 24 hours, respectively, at room temperature (25°C) under normal room fluorescent light in both glass and plastic containers.

VePesid Capsules must be stored under refrigeration 2°-8°C (36°- 46°F). The capsules are stable for 24 months under such refrigeration conditions.

HOW SUPPLIED

VePesid® (etoposide) For Injection
NDC 0015-3095-20 – 100 mg/5 mL Sterile, Multiple Dose Vial, 10's
NDC 0015-3084-20 – 150 mg/7.5 mL Sterile, Multiple Dose Vial
NDC 0015-3061-20 – 500 mg/25 mL Sterile, Multiple Dose Vial
NDC 0015-3062-20 – 1 gram/50 mL Sterile, Multiple Dose Vial

VePesid® (etoposide) Capsules
NDC 0015-3091-45 – 50 mg pink capsules with "BRISTOL 3091" printed in black in blisterpacks of 20 individually labeled blisters, each containing one capsule.

Capsules are to be stored under refrigeration 2°-8°C (36°-46°F).

DO NOT FREEZE

Dispense in child-resistant containers.

For information on package sizes available, refer to the current price schedule.

Capsules:
Manufactured by:
B.F. Scherer GmbH
Eberbach/Baden, Germany

Injection:
BRISTOL LABORATORIES
Oncology Products
A Bristol-Myers Squibb Co.
Princeton, New Jersey 08543
U.S.A.

Distributed by:
BRISTOL LABORATORIES
ONCOLOGY PRODUCTS
A Bristol-Myers Squibb Company
Princeton, NJ 08543
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1-800-482-6700

By ordering or accepting any goods, you agree to the following terms and conditions:

New Accounts: You may establish an account with OTN by calling toll-free 1-800-482-6700 and providing an account representative with proof of license (a copy of the Federal DEA license/State license must match ship to address). Subsequently, you will be required to submit a completed, signed credit application and agreement via mail or fax.

Orders: All orders are subject to acceptance by OTN or its agents at its principal place of business. Not withstanding any other provisions, whenever OTN, in its sole judgement, has any doubt as to buyers credit or ability to make payment in cash, OTN reserves the right to require payment in advance of shipment.

Shipping: Items are shipped prepaid by OTN. Orders for $100.00 or more are shipped free of charge. Orders for less than $100.00 are subject to a $15.00 service charge. (This charge does not apply to back-ordered items.) Drug items are shipped via overnight delivery to arrive no later than 3:30 p.m. the next business day. Supply items are shipped via FedEx® Express Saver in three days or less. Expedited delivery is available upon request for $25.00 as follows:
Drug orders are shipped to arrive by 10:30 a.m. the next business day. Notwithstanding the above, OTN's only obligation is to make reasonable commercial efforts and, in any event, it cannot be responsible for matters beyond its reasonable control. The above delivery schedule may not be available in certain geographic areas.

Title to merchandise passes to the buyer upon delivery by the carrier. The responsibility of OTN for the merchandise ceases when shipment is delivered and accepted.

Product Availability: Items in stock are available for immediate shipment. In the event of excess demand, or short supply, OTN may allocate its inventory among its members as it deems appropriate. OTN shall not be liable for failure to fulfill any order or to perform under any contract due to strike, fire, unavoidable accidents, inability to obtain supplies, contingencies of manufacturing, or other causes beyond its control. We reserve the right to discontinue and withdraw from the marketplace any product, product size, or packaging at any time without further obligation on the part of OTN.

Payment Terms: Purchases that remain unpaid past their invoice due date incur finance charges based on the outstanding balance calculated from the due date until paid at an Annual Percentage rate of 12% (8.5% in Alaska and Arkansas and 8% in Minnesota), or if lower, the maximum rate permitted under applicable law. In the event of any overpayment of finance charges, such overpayment shall be applied to the remaining portion of your balance or returned to you. If back payments are due, current orders may not be shipped until payments are received. OTN reserves the right to maintain a credit limit on all accounts.

Pricing: Prices are subject to change without notice. Prices billed are the prices in effect at the time the order is accepted by OTN. Prices are subject to all taxes, excises, or other charges levied by any government (national, state or local).

Any disputed prices need to be submitted in writing within 75 days of invoicing. Rebates and credits may be considered a discount and may need to be disclosed as required by applicable law. All manufacturer contract prices are effective within 5 business days upon OTN's receipt of the bid award notification from the manufacturer. Contract prices are subject to early termination upon notification by manufacturer.

Damages and Claims: Inspect all shipments immediately upon arrival. If you find broken or damaged goods, notify OTN by phone within five days of receiving the shipment. so that we may arrange for pick-up and replacement.

Returned Goods Policy:

1. OTN reserves the right to determine the eligibility of products to be returned for credit. Returns are subject to final review and evaluation by OTN, and will be processed in accordance with the returned goods policy in effect at the time the product was ordered.
2. All returns must be made to OTN accompanied by an itemized Return Materials Authorization Form and a signed statement that ensures that products were stored according to manufacturer specifications. A Return Materials Authorization Form can be obtained by calling the Customer Service Department at 1-800-482-6700.
3. Credit for returns will not be issued for product sold with the specific designation that it is non-returnable.
4. Because product storage conditions are not within our control once product leaves our facility, OTN has a "No Returns" policy on refrigerated items. Therefore, no credit for returns will be issued for refrigerated products.
5. Product not purchased from OTN will not be accepted for credit and/or return.
6. Supply items, except those shipped in error, are not eligible for credit and/or return.
7. Special Order items (i.e., items not listed in OTN Sourcebook), are not eligible for credit and/or return.
8. This returned goods policy applies to purchases in the original manufacturer's packaging and in the manufacturer's minimum quantity. Product that has been repackaged or is otherwise known as distressed merchandise, or product not in the original container, is not eligible for credit and/or return.
9. Please notify the Customer Service Department at 1-800-482-6700, of damages or shortages within five days of delivery, and note the damage or shortage on all delivery receipts or freight bills. Sign only for products actually delivered.
10. OTN will issue credit for authorized returned goods once received and processed by our warehouse. No deduction can be taken prior to that time.
11. Returns not due to OTN's error will be subject to a $25.00 handling fee.
12. OTN reserves the right to amend this policy by notification of the purchaser.

Expired Drug Return Policy:

1. OTN will accept expired drugs and issue credit in accordance with the manufacturer's expired drug return policies.
2. Expired products may be returned for credit only with prior authorization from OTN. Call 1-800-482-6700 and request an expired drug return form. The customer service representative will fax the form for completion.
3. Under no circumstances will OTN issue credit for return of expired drugs beyond one year of the expiration date.
4. OTN will review completed expired drug return forms and determine what is eligible for return.
5. OTN will fax what is/is not returnable along with the dollar amount of the credit. The amount of the credit will be based on customer's current price for the drug less 20%.
6. Credit will be issued once the completed form and drug is received and processed by the OTN warehouse.

Purchase for Own Use: Sales are made with the express understanding and agreement that merchandise is purchased for the sole use in the purchaser's medical practice, and is not intended to be sold or transferred for further sale or resale by retailers, wholesalers or other parties.

Sales Taxes: We are required by law to collect sales tax in certain jurisdictions. If appropriate we will, therefore, add the proper amount of tax (state, and, if any, local and transit) to your order.

Liability: OTN will not be liable under any contract, negligence, strict liability or other theory for any special, indirect, incidental or consequential damages or costs of procurement of substitute goods or services in connection with the subject matter of these terms and conditions or any products or the use, delivery or failure or delay of delivery thereof. OTN is not liable to any member for any loss, claim, or damage resulting from products or the use, delivery, or failure of delivery thereof, and the members hold OTN harmless for any such loss, claim, or damage.

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OTN

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